REMARKS

Claims 1, 2 and 4-42 are pending. Claims 20-31 and 33-42 are canceled herein, without prejudice or disclaimer. Claims 1, 2, 4-19 and 32 were rejected under 35 U.S.C. § 103.

Applicants gratefully acknowledge withdrawal of (1) the objection to the specification and (2) the rejections under 35 U.S.C. §§ 112, second paragraph and 102.

By amendment herein, the limitations of claim 2 have been incorporated into claim 1. Accordingly, claim 2 has been canceled. Further, as requested by the Examiner, claims 20-31 and 33-42, previously withdrawn from consideration, have been canceled herein, without prejudice or disclaimer. The amendments are made solely to expedite prosecution, are not intended in any way as an acknowledgment as to the correctness of the Examiner's position. Applicants reserve the right to file a continuation or divisional application directed to the subject matter of the canceled claims.

In view of the foregoing amendments and following remarks, reconsideration of the claims is respectfully requested.

Forms PTO-1449

Applicants thank the Examiner for re-sending the initialed 1449 forms submitted with the IDS on March 5, 2001.

35 U.S.C. § 103

Claims 1-19 and 32 stand rejected under 35 U.S.C. section 103(a) as allegedly obvious over Bartenschlager in view of EP 0693687 (hereinafter "Houghton") and U.S. Patent No. 5,372,928 (hereinafter "Miyamura"). Briefly stated, it is maintained that Bartenschlager demonstrates that a deletion of 60 amino acids rendered the protease nonfunctional and that further deletions were not necessary, albeit the reasons for the lack of protease activity were not clear. (Office Action, page 3). Thus, it is alleged that an amino acid deletion of more than 60 amino acids resulting in a non-functional protease is expected in view the fact that the claimed polypeptide contains the deletion of Bartenschlager. (Office Action, page 3). Further, it is again maintained that the missing elements are alleged to be disclosed by Houghton and Miyamura. (Office Action, page 4).

Applicants traverse this rejection and address the Examiner's allegations in turn.

A reference must be used for what it actually teaches as a whole. *See, e.g., In re Wesslau* 47 USPQ 391 (CCPA 1965) holding that "it is impermissible within the framework of section

103 to pick and choose from any one reference only so much of it as will support a given position, to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one of ordinary skill in the art." Thus, a reference must be taken for all that it teaches or suggests. *See, e.g., Bausch & Lomb, Inc. v. Barnes-Hind/Hydrocurve,* 230 USPQ 416, 420 (Fed. Cir. 1986). Similarly, the claims must be viewed as a whole.

Here, when viewed as a whole, it is clear the references in no way teach or suggest the polypeptides as claimed by Applicants. The pending claims are directed to polypeptides (i) that include a deletion of at least 200 amino acids of the N-terminal portion of NS3; (ii) that have a complete C-terminal portion of NS3; and (iii) in which the deletion functionally disrupts the catalytic domain. Thus, the claims are directed to specific polypeptides having the specified deletions and functions.

Bartenschlager fails entirely to teach or suggest NS3-containing polypeptides having the claimed characteristics. As acknowledged by the Examiner, Bartenschalger does not describe or demonstrate deletions of more than 60 amino acids of the N-terminal of NS3, let alone deletions of at least about 200 amino acids. Bartenschlager describes only N-terminal deletions of up to 60 amino acids and internal deletions including both N-terminal and C-terminal residues. Moreover, Bartenschlager does not teach or suggest that deletions of at least 200 N-terminal amino acids will disrupt the catalytic domain. (See, *e.g.*. FIG. 6B). Instead, this reference acknowledges that their attempts to map the boundaries of either the proteinase or helicase domains of NS3 failed:

> To map the 3' boundary of the proteinase, a panel of internal NS3 deletions lacking sequences predicted to encode the helicase activity was created. (Fig. 6A). ... As shown in Fig. 6B, all deletion constructs produced clearly visible amounts of precursor protein. However, in no case could processing products be detected either with longer exposures or in immunoprecipitations ... Currently, we cannot decide whether the deletions affected the proteinase activity or accessibility of the cleavage site or both ... (Bartenschlager, page 3840, right column)

Therefore, contrary to the Examiner's assertion, Bartenschlager's failure to delineate the functional regions of NS3 means that no conclusions can be drawn about what a 200 amino acid N-terminal deletion might do to NS3 function. Accordingly, the teachings of Bartenschlager would not have been expected to result in the claimed polypeptides.

Applicants also note that the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). The references must teach all the limitations of the claimed invention and, moreover, suggest the desirability of arriving at the claimed subject matter. (*See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023 (Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of along sought and difficult scientific goal was obvious" and *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.")

Thus, it is not Applicants' responsibility to point out special properties of the claimed polypeptides as maintained by the Office. (Office Action, page 4). Rather, the burden is on the Office to demonstrate how Bartenschlager teaches or suggests such a polypeptide. For the reasons noted above, Bartenschlager fails to suggest an NS3 polypeptide lacking at least 200 N-terminal amino acids (but including the C-terminal) in which the deletion functionally disrupts the catalytic domain. Simply put, there is no motivation in Bartenschlager to make the claimed deletions because the potential effects on proteinase and helicase functions were undetermined.

The secondary references do not cure the deficiencies of Bartenschlager. Indeed, neither Houghton and Miyamura disclose the claimed NS3 mutant polypeptides. Houghton is directed to combination HCV antigens comprising antigen from the core domain of HCV and an additional HCV antigen, for example C33c, an antigen extending from approximately amino acids 1192 to 1457 of NS3. Thus, unlike the claimed mutant polypeptides, C33c lacks C-terminal amino acids of NS3 (which itself extends from approximately 1050 to 1640 of an HCV polypeptide). For its part, Miyamura is silent as to any deletions in NS3. Thus, there is no description or demonstration in any of the references regarding an NS3 mutant polypeptide lacking more than 60 N-terminal amino acids, as is claimed by Applicants.

Further, the alleged "general knowledge" found in the specification that amino acids 1207-1278 of NS3 (page 3 of the specification) represent an immunodominant region for CD4+ cells, cannot support the obviousness rejection set forth on page 4 of the Office Action. It is improper to base on obviousness rejection on an allegation that the general level of skill in the art was high and, accordingly, the motivation is present. *See, e.g., In re Rouffet,* 47 USPQ2d 1453 (Fed. Cir. 1998). In the pending case, the alleged motivation to form pharmaceutical

compositions using the claimed polypeptides cannot derive from the knowledge that a particular region of NS3 is immunogenic because at least a portion of this region is not present in the claimed polypeptides. NS3 extends from approximately amino acids 1027 to 1657, numbered relative to an HCV-1 polypeptide. (See, page 28, lines 23-25 of the specification). At a minimum, the claimed polypeptides are lacking amino acids 1027 to 1227. Thus, one or more epitopes of the immunodominant region may be lacking and, as such, there is no motivation to combine the teachings of Bartenschlager and the secondary references and no reasonable expectation that immunodominant epitopes would be present in the claimed polypeptides.

In sum, there is nothing in any of the references that would lead one of skill in the art to combine them as suggested or that such a combination would reasonably lead one of skill in the art to the claimed subject matter. A *prima facie* case of obviousness has not been established and withdrawal of these rejections is respectfully requested.

CONCLUSION

In view of the foregoing amendments, Applicants submit that the claims are now in condition for allowance and request early notification to that effect.

Please direct all further communications regarding this application to:

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Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

1. (Twice Amended) An isolated mutant non-structural ("NS") HCV polypeptide comprising a polypeptide having a deletion [more than 60] at least 200 amino acids from the N-terminal portion of NS3, wherein said deletion functionally disrupts the catalytic domain of NS3 and further wherein said polypeptide comprises the C-terminal portion of NS3.

2. Canceled.

20-31. Canceled.

33-42. Canceled.